Sleep Oscillations and Their Blockage by Activating Systems

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Submitted: August 13, 1993
Accepted: November 18, 1993

There are three major oscillations in thalamocortical systems during the state of sleep with synchronization of the electroencephalogram: 1. Spindles (7 Hz to 14 Hz) are generated in the thalamus at sleep onset and are blocked during arousal or rapid-eye-movement sleep by cholinergic systems that decouple the synchronizing network of the reticular thalamic nucleus. 2. Delta potentials (1 Hz to 4 Hz) appear during late stages of electroencephalogram-synchronized sleep. At the thalamic level they are produced by the interplay between two intrinsic currents of neurons with cortical projections. Delta rhythm is suppressed by cholinergic and noradrenergic systems. 3. A slow oscillation (< 1 Hz) is generated in the cerebral cortex and has a pivotal role in grouping the thalamic-generated sleep rhythms within wave-complexes recurring periodically, every two to five seconds. The slow rhythm is blocked by cholinergic and noradrenergic projections. Sleep rhythms consist of long-lasting inhibitory components that obliterate synaptic transmission and disconnect the brain from the outside world.

Key Words: electroencephalogram, sleep, oscillations, thalamus, cerebral cortex, intracellular recordings

This article reviews some data on the cellular substrates of thalamic and cortical oscillations appearing on the electroencephalogram (EEG) during different stages of quiescent sleep state with EEG synchronization (Steriade 1993). Although various isolated neurons may oscillate due to their intrinsic properties (Llinás 1988), such stereotyped events elicited in single cells by manipulations of their membrane potential (V_m) are transformed into patterns resembling the sleep rhythms of a living animal by interactions with other neurons in networks consisting of billions of synaptically coupled thalamic and cortical cells.

Figure 1 shows that the more intact the brain, the more complex sleep rhythms are produced by interactions between different structures. The isolated reticular thalamic nucleus generates spindle rhythmicity even after its isolation from other thalamic nuclei and the cerebral cortex. As well, the delta oscillation is seen in completely disconnected dorsal thalamic nuclei. When the activity of thalamocortical systems is recorded after a transection at the upper brainstem level, both spindles and delta rhythms appear. Finally, in the intact brain of anesthetized animals and during natural sleep, different sleep rhythms are combined and delta waves are grouped within a slow rhythm.

Data on the neuronal substrates of various types of sleep oscillations, mainly resulting from intracellular recordings *in vivo* of cat thalamic and cortical neurons, are briefly summarized below.

Spindles, a network-generated thalamic oscillation at the onset of sleep

Spindles appear with mirror (inverse) images in reticular thalamic neurons, using γ aminobutyric acid (GABA) as inhibitory neurotransmitter, and in their thalamocortical targets, using glutamate as excitatory neurotransmitter (see circuit in Figure 2A). In the former, a spindle sequence consists of rhythmic (7 Hz to 14 Hz) spike-bursts superim-

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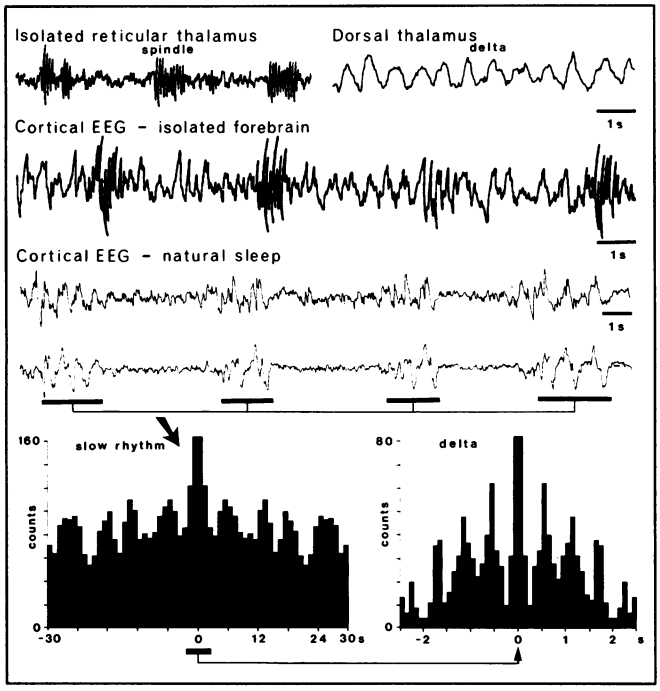

Fig. 1. Oscillations of brain electrical activity and their increasing complexity from the isolated thalamic and cortical structures to the whole brain. Recordings in different types of experiments on cats. The isolated reticular thalamic nucleus generates spindles. The dorsal thalamus disconnected from the cerebral cortex displays delta rhythm. In the intralaminar thalamic nucleus of an isolated forebrain spindle sequences occur and, between them, delta waves appear. During natural sleep, delta waves are grouped within sequences recurring with a slow rhythm (upper trace from the cortical surface, lower trace from the cortical depth). The slow rhythm is also illustrated in the left autocorrelogram. The delta rhythm is shown in the right autocorrelogram, representing an expanded part of the left one. Modified from Steriade et al (1987); Paré et al (1987); Steriade et al (1991); and Steriade et al (1993c).

posed on a slowly growing and decaying depolarizing envelope, whereas in the latter spindles are mainly inhibitory postsynaptic potentials (IPSPs), occasionally giving rise to spike-bursts that are transferred to cortical neurons and excite them within the frequency range of spindles (see Figure 2B). The idea that the reticular thalamic nucleus is the spindle pacemaker is based on: 1. the abolition of EEG spindles in thalamocortical systems disconnected from the reticular nucleus or naturally devoid of connections with this nucleus (Steriade et al 1985; Pare et al 1987); and 2. the preservation of these oscillations in the deafferented reticular nucleus (Steriade et al 1987). The failure to obtain spindles in *in vitro* recordings of the isolated reticular nucleus (von Krosigk et al 1993) is probably due to the absence of a critical mass of reticular thalamic neurons that is necessary to generate synchronized oscillations. The proposal that the isolated reticular thalamic nucleus generates spindle rhythmicity (Steriade et al 1987) is strengthened by models of reticular thalamic neurons with mutual slow inhibition that display synchronous oscillatory activity within the frequency range of spindles (Wang and Rinzel 1993, Destexhe et al 1994).

Since spindles are characterized by prolonged IPSPs in thalamocortical cells (see Figure 2B), this oscillation is effective to obliterate the synaptic transmission of incoming volleys and, thus, to produce unresponsiveness which occurs during the stage of falling asleep.

That the thalamus is the first relay station where afferent signals are inhibited from the very onset of sleep is shown by drastic diminution of postsynaptic events in thalamic nuclei, despite no changes in the magnitude of the presynaptic components reflecting the activity in incoming axons (Steriade 1991).

Spindles are blocked at the very site of their genesis, the reticular thalamic neurons, by setting into action mesopontine cholinergic nuclei (Hu et al 1989). The cholinergic hyperpolarization of reticular cells is produced by activation of a potassium conductance (McCormick and Prince 1986). The blockage of spindles in reticular thalamic cells upon arousal and rapid-eye-movement (REM) sleep results in the suppression of IPSPs in cortical-projecting thalamic neurons. Consequently, full synaptic responsiveness is recovered in thalamocortical systems during these brain-active states. Besides, the increased firing rates of corticothalamic neurons during waking and dreaming sleep (Steriade 1978) leads to further activation of thalamic neurons that is mediated by glutamate metabotropic receptors (McCormick and von Krosigk, 1992).

Delta, an intrinsic oscillation of thalamocortical cells

With deepening of sleep, spindles are progressively replaced by an EEG oscillation at a lower frequency (1-4 Hz), termed delta rhythm. Waves within this frequency range arise partially in the cerebral cortex, as inferred from their survival after extensive thalamic lesions (Villablanca 1974; Steriade et al 1993d). However, the thalamus also plays a major role in the genesis of delta oscillation. Indeed, thalamocortical neurons display the delta rhythm which results from the interplay between two intrinsic currents of these cells, as demonstrated *in vitro* (McCormick and Pape 1990a; Leresche et al. 1991) and *in vivo* (Steriade et al 1991; Curró Dossi et al 1992).

This interplay critically depends upon the hyperpolarization of thalamocortical neurons, about 10 mV more negative than the V_m at which spindles are generated. Depolarization brings thalamic cells out of the voltage range where delta is generated and removal of the depolarizing current sets back the neurons in the oscillatory mode (see Figure 3A). The

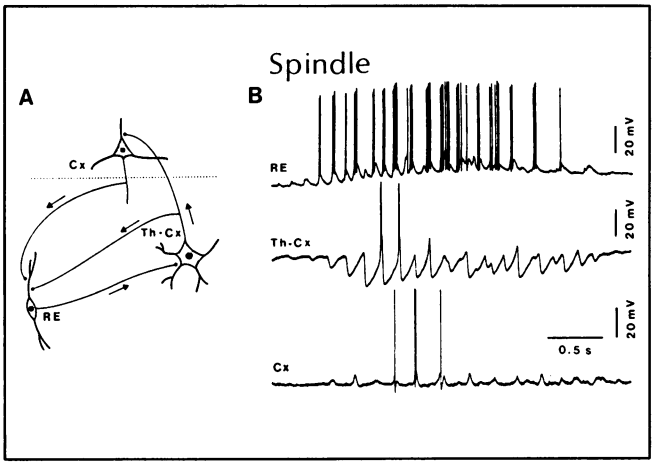

Fig. 2. Cellular bases of spindle rhythm. *A*, circuit diagram of reticular thalamic (RE), thalamocortical (Th-Cx), and cortical (Cx) neurons involved in the genesis of spindle waves. Arrows indicate the direction of axonal projections. *B*, intracellular recordings of one sequence of spindle oscillations in these cellular types in cats under barbiturate anesthesia. See text for further description. Modified from Steriade and Deschênes (1988).

hyperpolarization of thalamic cells is mainly due to the diminution, during sleep, of activating impulses generated by brainstem cholinergic and noradrenergic neurons (see Steriade and McCarley 1990). It was postulated that the transition from spindles to delta rhythms is due to a progressive hyperpolarization of thalamocortical neurons across the state of EEG-synchronized sleep (Steriade et al 1991). This hypothesis is supported by EEG recordings in intralaminar thalamic nuclei, showing prevalent spindles at sleep onset and their progressive replacement by delta patterns at later stages of sleep (Lancel et al 1992).

However efficient the thalamocortical intrinsic (voltage-gated) currents are in generating potentials within the frequency range of EEG delta waves, this oscillation can be reflected at the macroscopic EEG level only if pools of oscillating thalamic neurons are synchronized (Steriade et al 1991). This process can be achieved locally (see Figure 3B) in some thalamic nuclei that have the circuitry allowing the coupling of relay thalamic neurons (Nuñez et al 1992; Soltesz and Crunelli 1992). For more widespread thalamic synchronization, the reticular thalamic nucleus is the ideal candidate to subserve potentiation and synchronization of delta rhythm because: 1. it consists of inhibitory cells which may set the V_m of thalamocortical cells at the level where delta rhythm is generated; and 2. its constituent neurons have widespread thalamic projections and, thus, may unite into coherent assemblies neurons that are otherwise independent oscillators.

Delta oscillaton is suppressed by the action of brainstem cholinergic (Steriade et al 1991) and noradrenergic (McCormiclc and Pape 1990b) systems. It should be mentioned that only cholinergic and glutamatergic modulatory systems can transform delta oscillation into a tonic activated pattern during both waking and dreaming sleep because monoaminergic neurons are silent during REM sleep (Steriade and McCarley 1990).

The slow oscillation in corticothalamic systems

Recently, we reported that delta potentials are grouped within wave-sequences which recur periodically, every two to five seconds, during natural sleep of cats and humans (Steriade et al 1993c). Intracellular recordings in anesthetized animals revealed that an overwhelming (88%) proportion of neocortical pyramidal neurons recorded from sensory, associational and motor areas and electrophysiologically characterized as either regular-spiking or intrinsically-bursting, display this slow oscillation at <1 Hz, mainly ≈0.3 Hz (see Figure 4). The slow cellular rhythm appears in close time-relation with EEG waves recorded from the cortical surface and depth (Steriade et al 1993cd).

While the genesis of the slow oscillation is independent of the thalamus, as it survives total lesions of nuclei projecting to the areas where recordings are performed, the cortical rhythm potently influences the activity of both reticular thalamic and thalarnocortical neurons (Steriade et al 1993b). At the reticular thalamic level, the cortical oscillation is reflected as depolarizing-hyperpolarizing sequences, much the same as it appears in cortical cells (see Figure 4), despite great differences in the intrinsic properties of these two neuronal types. In thalamocortical neurons, the slow oscillation appears as a periodic (≈0.3 Hz) dampening of delta oscillation (see Figure 4). This quasi-rhythmic reduction of thalamic delta potentials is presumably due to an increase of membrane conductance due to the periodic arrival of cortical excitatory and reticular thalamic inhibitory inputs converging onto thalamocortical cells (Steriade et al 1993b).

The slow oscillation is suppressed for ten to 15 seconds by stimulating the pedunculopontine tegmental cholinergic nucleus or the locus coeruleus noradrenergic nucleus (Steriade et al 1993a) and is replaced by tonic firing (top trace in Figure 4). This effect is accompanied by an EEG activated reponse with a similar time-course.

CONCLUSIONS

The above data show that sleep oscillations are highly orchestrated in interacting thalamic and neocortical networks and that they are regulated by brainstem modulatory systems. Although we have begun to understand in recent years some of the oscillatory mechanisms at the single cell level, we should further investigate sleep rhythms by means of simultaneous intra- and extracellular recordings in multiple sites

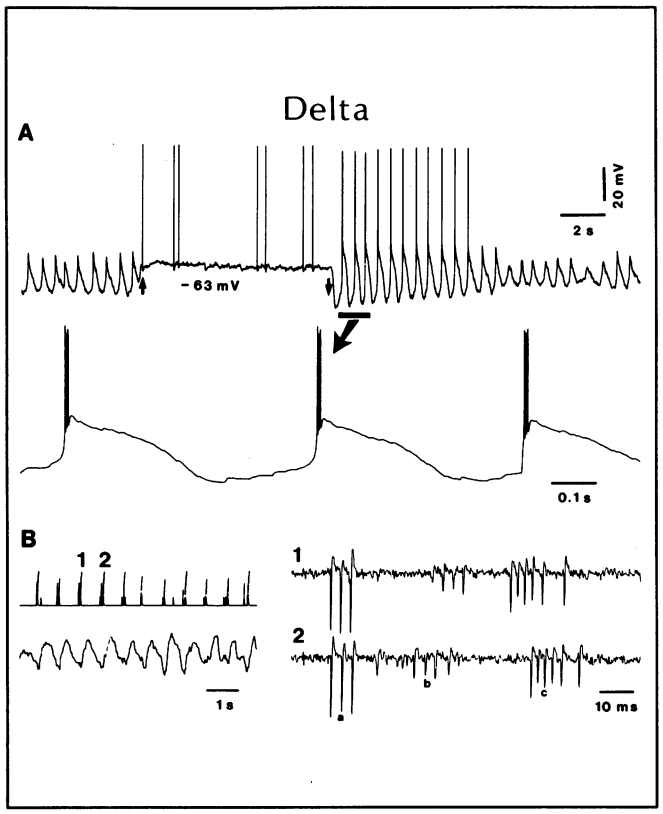

Fig. 3. **Cellular substrates of delta oscillation. *A*, voltage-dependency of delta oscillation. Intracellular recording of cat lateroposterior (LP) thalamocortical cell after decortication of areas projecting to LP nucleus (urethane anesthesia). The cell oscillated spontaneously at 1.7 Hz. A 0.5 nA depolarizing current pulse (between arrows) prevented the oscillation and its removal set the cell back into the oscillatory mode. *B*, synchronization of delta activity in three thalamocortical cells, simultaneously recorded through the same microelectrode. Epochs 1-2 of left part are expanded at right, with original spikes of three spikes. Modified from Steriade et al (1991).**

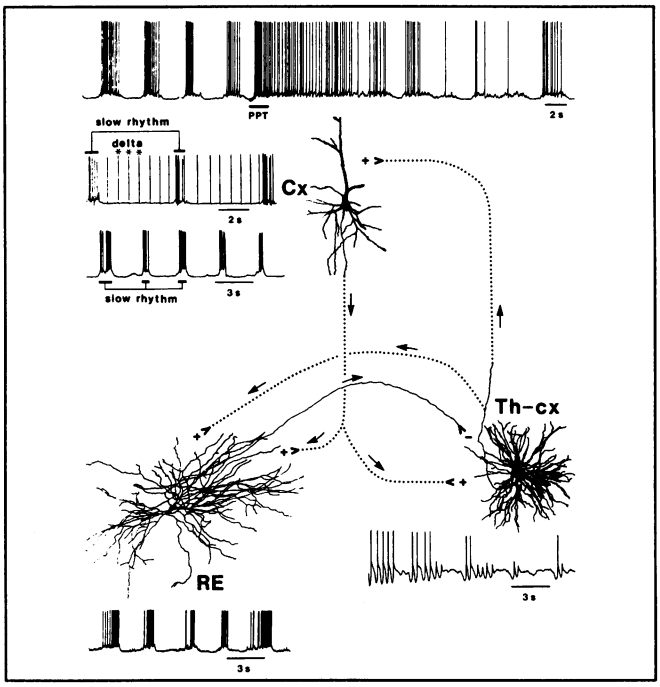

Fig. 4. **The slow sleep oscillation and its suppression by brainstem core cholinergic systems. Intracellular recordings in anesthetized cats (modified from Steriade et al 1993a-d). Also shown are intracellularly stained cortical and thalamic cells (modified from Steriade and Deschenes 1984; and Steriade et al 1993c). Top trace shows the slow oscillation (0.3 Hz) in cortical cell recorded from area 5. A brief pulse-train (30 Hz) to the cholinergic pedunculopontine tegmental (PPT) nucleus (horizontal bar) transiently suppressed the slow cortical oscillation and replaced it by tonic firing. This effect was associated with an EEG response with a similar time-course and was blocked by a muscarinic antagonist (data not shown; see Steriade et al 1993a). Below is a summary diagram depicting several aspects of sleep oscillations in interacting cortical and thalamic networks. Direction of axons is indicated by arrows and excitatory or inhibitory signs are indicated by + or -. Two neocortical (Cx) neurons, recorded from area 5, show a slow rhythm (0.17 Hz in first trace, 0.3 Hz in bottom trace). In the first trace, note the appearance, between the depolarizing envelopes of the slow rhythm, of clock-like action potentials at the delta (1.5 Hz) frequency and presumably arising in thalamocortical neurons. The reticular thalamic (RE) neuron displays the slow oscillation (0.3 Hz). The thalamocortical (Th-cx) cell displays delta oscillation (2.5 Hz) that tends to dampen periodically, within the frequency range of the slow rhythm (0.2 Hz to 0.3 Hz), due to an increase in membrane conductance resulting from the converging excitatory inputs arising in cortical neurons and inhibitory inputs from RE neurons.**

of thalamic nuclei (Steriade and Contreras 1993) and neocortical areas (Amzica and Steriade 1993). These studies, still in progress, reveal a dramatic coherence between the cortex and the thalamus during EEG-synchronized sleep, with time lags in crosscorrelograms ranging from less than 10 ms to more than 100 ms. However, the complexity of thalamocortical networks by far exceeds the power of electrophysiological recordings and, therefore, computer simulations (see Churchland and Sejnowski 1992) are required to investigate rhythms similar to those observed in living animals by using realistic models of cortical and thalamic networks.

ACKNOWLEDGEMENTS

This study was supported by a grant from the Medical Research Council of Canada.

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